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Re: Reply to Teva's Response to Citizen Petitions filed by Ranbaxy Laboratories Limited and IVAX Pharmaceuticals, Inc.
Docket Nos. 2005P-0046 and 2005P-0008

Ranbaxy Laboratories, Inc. ("Ranbaxy") submits this reply to the June 8, 2005, Response ("Teva Response") filed by Teva Pharmaceuticals USA ("Teva") to the citizen petitions filed by Ranbaxy and IVAX Pharmaceuticals, Inc. ("IVAX"). In its petition, Ranbaxy requests that FDA refrain from the approval of any ANDA for simvastatin 80 mg tablets until Ranbaxy's 180-day exclusivity has expired. Ranbaxy believes it is entitled to this exclusivity by virtue of being the first to file an ANDA for Merck's Zocor, with a paragraph IV certification to two listed patents, U.S. Patent RE 36,481 ("the '481 patent") and U.S. Patent RE 36,520 ("the '520 patent"). IVAX makes a similar request for other simvastatin drug products. Teva has now filed a response to these petitions.

Teva argues that the citizen petitions filed by Ranbaxy and IVAX should be denied because (1) the Merck patents at issue were improperly listed; (2) errors that occur in listing patents should be subject to correction; and (3) 180-day exclusivity should not be based on patents that do not qualify for listing in the Orange Book. Teva Response at 1. Each of Teva's arguments is either incorrect or irrelevant to the issue of whether FDA may revoke Ranbaxy's exclusivity. The patents as to which Ranbaxy was the first to file a paragraph IV certification were not improperly listed; rather, it was the withdrawal of the listing that was in error. Second, FDA's ability to correct improper patent listings is not impeded by granting Ranbaxy's Citizen Petition. Third, because 180-day exclusivity is intended to serve as an incentive for a generic applicant to challenge wrongly listed patents, Hatch Waxman envisions that improperly listed patents should, and in fact often do, give rise to 180-day exclusivity. Accordingly, Teva fails to advance any legitimate reason for denying Ranbaxy the 180-day exclusivity to which it is entitled.

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Further, Teva fails to address several of the most important issues. It does not discuss FDA's regulation delaying delisting where litigation has begun and the policy and legal concerns that motivated it. It speaks only to delisting improperly-listed patents, ignoring the fact that FDA has said on multiple occasions that it does not want to have to determine whether patents are improperly listed. It ignores the implications of allowing indiscriminate delisting to extinguish exclusivity, which could affect exclusivity for many different drugs. It ignores the potential to add even more complexity and gamesmanship to 180-day exclusivity, by allowing innovators to decide whether exclusivity will be awarded, and to influence, in some circumstances, the generic company to which it will be awarded. It also creates incentives for generic companies to try to influence innovators to their own advantage, as it appears that Teva has done here.

Moreover, Teva's response illustrates that FDA lacks any procedure for ensuring that legitimate exclusivities are not extinguished by the delisting of patents. This is a real concern for companies like Ranbaxy that can be seriously harmed by the unexplained and unexpected withdrawal of the exclusivity they have earned by being the first to file a paragraph IV certification.

The Merck Patents Were Improperly Delisted.

As Ranbaxy demonstrated in its May 20, 2005 response ("Ranbaxy Response"), FDA cannot assume that the delisting of a patent signifies that the patent was wrongly listed in the first place. Ranbaxy Response at 4-5. Merck's delisting is an example of an improper delisting.

Teva's sole support for its argument that the Merck patents were improperly listed consisted of a lawyer's letter to FDA, which baldly asserts that the '481 patent and the '520 patent claim compounds "which are said to be metabolites of simvastatin." Teva Response, Exh. A, at 1. Teva does not explain why, or by whom, these compounds were said to be metabolites. Instead, it applies a "said to be" standard for determining whether patents are properly listed.

In fact, the '481 and the '520 patents claim a number of compounds themselves, and in pharmaceutical compositions, that are created when Zocor is manufactured. Ranbaxy Response at 4; Declaration of William D. Hare at 4; Declaration of Dr. Tippasandra Gowripathi Chandrashekhar at 2. Ranbaxy's testing confirmed these patented compounds are present in commercially available Zocor. Id.

In the preamble to its August 18, 2003 rule identifying which patents should not be listed in the Orange Book, FDA explained that "[a] metabolite is the chemical compound that results after the active ingredient of the drug has been broken down inside the body." Applications for FDA Approval to Market a New Drug; Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying

That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, Final Rule, 68 Fed. Reg. 36,676, 36,680 (June 18, 2003). The compounds covered by the '481 and '520 patents are present in Zocor before the drug is administered to the patient and broken down in the body. [1]

In summary, Teva's assertion that the patents should not have been listed is contradicted by the ample and unrebutted evidence that the '481 and '520 patents claim compounds present in Zocor. Under Teva's logic, because the patents were properly listed, Ranbaxy is entitled to 180-day exclusivity under Hatch Waxman. Were FDA to refuse to recognize Ranbaxy's 180-day exclusivity because of Teva's attempts to eliminate exclusivity on simvastatin, and Merck's subsequent error in requesting the withdrawal of these patents, FDA would be wrongly depriving Ranbaxy of this right.

FDA Can Recognize A First Filer's Exclusivity and Allow NDA Holders to Correct Listing Errors.

Teva also argues that "[e]rrors that occur with respect to the listing of patents should always be subject to correction." Teva Response at 1. Ranbaxy agrees. Correction of Orange Book listings errors and the right to exclusivity, however, can be treated as two analytically distinct issues, as FDA does when an ANDA applicant successfully defends a patent infringement suit. The correction of errors does not preclude 180-day exclusivity, nor does 180-day exclusivity preclude the correction of errors. See Ranbaxy Response at 3. FDA can advance both objectives, either by delisting the patent but continuing to recognize the 180-day exclusivity and so inform subsequent applicants, or by accepting an NDA holder's request to delist but deferring delisting until the 180-day exclusivity expires.

Hatch Waxman Contemplates That Challenges to Wrongly Listed Patents Will Give Rise to Exclusivity.

The fundamental error underlying Teva's argument that the statute does not support the award of 180-day exclusivity based on patents that do not qualify for listing is that it turns Hatch Waxman on its head. The purpose of the paragraph IV process and award of 180-day exclusivity is to make sure that patents that should not be barriers to competition do not delay entry of generic drugs. A patent listing in the Orange Book is a statement that the listed patent claims the drug, and it puts a potential generic competitor on notice that it must await the expiration of the patent or challenge it and risk litigation. This is as true for an improperly-listed patent as it is for a properly-listed patent. Thus, an improperly-listed patent may function as a barrier to

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1. Even if the patents had claimed metabolites, contrary to the suggestion in the Lee letter attached to Teva's response, they would have been properly listed. Nothing in the 2003 final rule on patent listing required NDA holders with NDAs approved before the effective date to remove patents that could not be listed following the enactment of the new rules. FDA's regulation clarifying that certain patents, including metabolite patents, should not be listed by NDA holders was effective as of August 18, 2003. 68 Fed. Reg. 36,676, 36,696 (June 18, 2003). FDA specifically declined to make the regulation retroactive, in noting that to apply the final rule retroactively "'would risk upsetting legitimate expectations held by those who had relied on our earlier interpretation of the act.'" Id. Here, both the listing and Ranbaxy's paragraph IV certification preceded the effective date of the regulation.

competition, and it is as important to provide an incentive for generic competitors to challenge those patents as it is to provide an incentive to challenge correctly-listed patents. For this reason, Teva's argument that it would be "bad policy" to base exclusivity on paragraph IV certifications to improperly listed patents cannot be correct. Teva Response at 2.

Teva's statement that it would be "legally improper" to grant exclusivity based on patents that do not claim the listed drug is equally incorrect. Id. Exclusivity does not rest on the appropriateness of the initial listing; instead, it arises from the challenge to a listed patent. The statute conditions exclusivity purely on submission of a paragraph IV certification. Thus, it plainly contemplates that exclusivity may be based on an improperly listed patent. FDA recognized this intent when it determined that it would delay delisting in order to preserve 180-day exclusivity when the first applicant successfully defended a patent suit. 21 C.F.R. § 314.94(a)(12)(viii)(A). In those circumstances, even an invalid patent remains listed. FDA similarly should seek to fulfill the purposes of Hatch Waxman when the first applicant succeeds in challenging the patent without need for litigation.

The weakness of Teva's approach is further highlighted in a situation in which circumstances change after the NDA holder receives a paragraph IV notification, and, for example, the paragraph IV notification make a strong unenforceability argument sufficient for the NDA holder to realize it can no longer enforce its patent and therefore requests that it be removed from the Orange Book. In such a case, there is no error either in the listing or the delisting of the patent, but Teva's rationale offers no principled guidance for deciding whether to continue to recognize or withdraw exclusivity.

Furthermore, Teva does not address the situation in which the patent is appropriately listed but inappropriately delisted. Because Teva's approach conditions exclusivity on the appropriateness of the listing, it logically follows that the converse must also be true: if a patent was correctly listed in the first place, then the first-filer is entitled to exclusivity, even if the patent is subsequently improperly delisted. Of course, this approach would require FDA to make a judgment about the propriety of the listing.

Ranbaxy realizes that FDA seeks to avoid making judgments about the propriety of listing specific patents and, presumably, will continue to do so. In those circumstances, FDA should follow a policy that does not upset legitimate expectations and penalize an ANDA applicant that, like Ranbaxy, reasonably relied on the NDA holder's certification that the listed patent claims the drug.[2]

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2. FDA has sought to exercise a ministerial role regarding patent listing decisions and courts have allowed it to maintain that position in part because parties can sort out their respective rights in patent infringement suits. See, e.g., aaiPharma Inc. v. Thompson, 296 F.3d 227, 241 (4th Cir. 2002); Watson Pharms. Inc. v. Henney, 194 F. Supp. 2d 442, 445 (D.Md. 2001). By contrast, delisting decisions cannot be adjudicated in patent infringement suits. While a party can challenge a listing decision in court, FDA has the final say on exclusivity when it comes to delisting. Accordingly, it is particularly important that it not exercise this authority by delegating to the NDA holder the unfettered ability to deprive a party of its exclusivity.

Policy Weighs Against Withdrawal of Exclusivity.

Teva also asserts that recognizing 180-day exclusivity when a patent has been delisted will lead to absurd results and a rule that makes no sense. Teva Response at 1. Teva, does not, however, explain why this should be so. Indeed, Teva confines its argument to noting that FDA decided to delist a metabolite patent for the drug nefazadone even though Teva was the first ANDA applicant to file a paragraph IV certification to a listed patent. Teva Response at 4. Teva acquiesced in that decision and elected not to file a citizen petition, apparently because it was aware the patent involved a metabolite. Id. Teva's posture in that situation, therefore, is clearly distinguishable.[3] Moreover, FDA was not then presented with the arguments raised by Ranbaxy and IVAX here.[4]

Teva neither addresses the legal arguments presented by Ranbaxy and IVAX, nor does it take issue with the policy objectives advanced if FDA recognizes Ranbaxy's entitlement to 180-day exclusivity, see Citizen Petition filed on behalf of Ranbaxy Laboratories Limited (Feb. 1, 2005) ("Ranbaxy Citizen Petition") at 6-8; Ranbaxy Response at 5-9. In fact, Teva's response illustrates how easily the process could be abused to deprive a generic applicant of its exclusivity. Teva appears to have made its demand that Merck withdraw these patents without having had to make any showing as to the propriety of the listing. Merck was not required to provide any explanation, let alone a showing, of the basis for the request to delist the patent. In short, there is nothing to prevent an NDA holder, by itself or in concert with a generic company, from withdrawing a listing simply to deny a first filer its exclusivity.[5] Yet, an FDA decision to withdraw exclusivity would have serious repercussions for Ranbaxy. Companies intent on undermining a first filer's position in the market will have a significant weapon unless FDA determines that it will not withdraw the first filer's exclusivity.

Teva's response indicates that delisting controversies can arise, at least in significant part, because a generic drug company that did not manage to be the first-to-file seeks to eliminate the first-to-file status of an applicant who successfully challenged listed patents. That Teva should desire to take advantage of the system by eliminating the incentive provided by the Hatch Waxman Act is understandable; but FDA should not allow it to succeed. Ranbaxy Citizen Petition at 3.

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3. Though Teva here says exclusivity cannot be based on an improperly listed patent, it has received exclusivity for an improperly listed patent. Teva's exclusivity for mirtazapine was recognized by FDA even after a court decided that the patent as to which Teva was the first to file a paragraph IV certification did not claim an approved use of the drug. Letter from Gary Buehler, Director, FDA Office of Generic Drugs, to Mr. Tim Gilbert (Feb. 24, 2003) (copy attached).

4. Even if the two situations were analogous, FDA is not precluded from adopting a different approach in these circumstances. See, e.g., Paralyzed Veterans of America v. Secretary of Veterans Affairs, 345 F.3d 1334, 1353 (Fed. Cir. 2003) ("[A]n agency may change its interpretation of an underlying statutory provision even absent alteration in that provision, so long as the reason for the change is explained . . . ."); Springfield Inc. v. Buckles, 292 F.3d 813, 819 (D.C. Cir. 2002) ("[A]gency views may change.").

5. Ranbaxy does not in any way suggest that any improper motive underlay Merck's decision to delist the patents at issue here.

In sum, as Ranbaxy has explained, refusing to recognize a first-filer's exclusivity will cause direct and immediate harm to the ANDA applicant, create incentives to delay entry by a generic applicant due to uncertainty, provide an opportunity for anticompetitive arrangements between an NDA holder and other generics and also accord NDA sponsors leverage over the generic who is the first to file a paragraph IV certification. Ranbaxy Response at 8. By contrast, refusing to recognize a first-filer's exclusivity will reward gamesmanship by other generic manufacturers and provide an incentive to generic manufacturers to shift resources to patent listing games from research for new generic products.

Conclusion

As Ranbaxy has demonstrated, a request to delist a patent does not mean that there was an error in the initial listing, or that the request to delist was made without ulterior motives, and FDA may not assume that they do. Adopting a rule that would deprive the first ANDA applicant of its 180-day exclusivity when an NDA holder seeks to delist a patent is manifestly unjust especially when that request is triggered, at least in part, by a request from a generic competitor that failed to obtain exclusivity. Here, for instance, it would reward Teva, at the expense of Ranbaxy and IVAX, though Ranbaxy and IVAX undertook the early efforts to design a non-infringing generic. Not only is this result unfair and contrary to law, it also creates the opportunity for anti-competitive conduct and increases the potential for consumer harm.

Respectfully submitted,

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 24 2003

Gilbert's
Attention: Mr. Tim Gilbert
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OGD Control # 03-107

Dear Mr. Gilbert:

This responds to your January 31, 2003, letter regarding FDA's treatment of ANDAs for mirtazapine in light of the agency's January 28, 2003, decision regarding 180-day exclusivity for pending ANDAs for gabapentin. Both the gabapentin and mirtazapine ANDAs raise questions related to whether an ANDA applicant may be eligible for 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) with respect to a patent that does not claim an approved use of the listed drug. Your concern is that FDA is treating these ANDAs - which you believe are similarly situated - in an inconsistent fashion. The agency has reviewed the record concerning the gabapentin and mirtazapine ANDAs, and your analysis, and has concluded that the decisions are warranted by the facts and are not inconsistent.

The agency is aware that on February 14, 2003, Torpharm sued FDA in the U.S. District Court for the District of Columbia over FDA's decisions related to the approval of gabapentin ANDAs. This response to your January 31, 2003, letter is being issued subsequent to that lawsuit. However, you should be aware that the agency had prepared its response regarding the differences between the gabapentin and mirtazapine situations before the February 14, 2003, lawsuit was filed. A February 13, 2003, letter from Organon requesting delisting of the '099 patent delayed issuance of the letter while the agency considered the effect, if any, of this request on 180-day exclusivity. The agency revised its letter to address the delisting issue, as described below.

As you know, FDA has determined that no gabapentin ANDA applicant is eligible for 180-day exclusivity as to U.S. Patent Number 5,084,479 (the '479 patent). FDA's determination that no ANDA applicant is eligible for 180-day exclusivity as to the '479 patent was based upon its conclusion that no applicant could legally maintain its paragraph IV certification as to that patent (and thus the patent could be removed from the Orange Book). This outcome is a consequence of the representation by Pfizer, Inc., the holder of the approved NDA for gabapentin capsules and the '479 patent, to FDA on December 13, 2002, disavowing any claim that the '479 patent covered the approved use of gabapentin – epilepsy (as opposed to the unapproved use – neurodegenerative diseases). This representation was confirmed in later correspondence with Pfizer, as well as in the findings of Judge Huvelle in *Purepac Pharmaceutical Co. v. Thompson*, No. 02-1657 (D.D.C. Dec. 16, 2002). The Federal Circuit also confirmed that the '479 patent

does not claim an approved use of gabapentin in *Warner-Lambert v. Apotex, Inc.*, No. 02-1073 (Fed. Cir. Jan. 16, 2003).

The mirtazapine situation is materially different. As you note, a district court has found in private patent infringement litigation that U.S. Patent No. 5,977,099 (the '099 patent) claims only an unapproved use for mirtazapine, not an approved use for which the ANDA applicants were seeking approval. *Organon, Inc. and Akzo Nobel N.V. v. Teva Pharmaceuticals, Inc.*, C.A. 01-2682 (Dec. 18, 2002 D.N.J.); *appeal docketed*, CA 03-1218 (Fed. Cir.). In addition, on February 13, 2003, counsel for Organon notified FDA that, although Organon still believes the '099 patent meets the requirements of section 505(b) of the Act for listing in the Orange Book, "[n]onetheless, Organon herewith requests the '099 patent be removed from the Orange Book." However, unlike with the '479 gabapentin patent, there has been no admission by the patent holder to FDA that the patent does not claim an approved use. Likewise, there has been no litigation involving FDA in which the court has expressly found that a section viii statement is the correct submission for the listed patent.

You argue that the gabapentin and mirtazapine situations are nevertheless the same and require the same outcome. Your position is that, to be consistent, FDA either 1) must require all mirtazapine ANDA applicants to now change existing paragraph IV certifications under section 505(j)(2)(A)(vii) to the '099 patent to section viii statements under section 505(j)(2)(A)(viii), and deny any applicant 180-day exclusivity as to that patent, or 2) must reverse its decision that no gabapentin ANDA applicant is eligible for 180-day exclusivity as to the '479 patent.

FDA disagrees. These are not analogous situations, and do not require the same regulatory treatment. As Judge Huvelle noted, the gabapentin situation involved "unique factual circumstances" that warranted special treatment by the court. In that case, the court found – in part on the basis of the use statements addressing the scope of the '479 patent - that the NDA sponsor never intended to assert that the '479 patent claims the approved use of the listed drug. In addition, as the court noted, Pfizer admitted as much in its December 13, 2002, letter to FDA. Therefore, the district court found that an ANDA applicant was entitled to file a section viii statement to that patent. In the mirtazapine case, we have no such admission to FDA by the NDA sponsor, and no specific court decision regarding the submission of a section viii statement.

Neither Judge Huvelle's narrow decision based on unique factual circumstances nor FDA's January 28, 2003, decision requires a change in established FDA practice regarding 180-day exclusivity. FDA's practice under section 505(j)(5)(B)(iv) and 21 C.F.R. § 314.107(c) is to grant 180-day exclusivity to the ANDA applicant that was first to file a valid paragraph IV certification to a listed patent, and for that exclusivity to be triggered, in certain cases, by a court decision in litigation resulting from a paragraph IV certification finding the patent invalid or not infringed. If the triggering court decision finds the patent invalid, FDA will leave the patent in the Orange Book for 180 days to give the first applicant the benefit of its exclusivity. 21 C.F.R. 314.94(a)(12)(viii); 59 Fed. Reg. 50338, 50348 (Oct. 3, 1994). As FDA explained in its rulemaking, to permit removal of the patent immediately upon a court decision of patent invalidity would deprive the first applicant of the benefit for which it is eligible by being first to challenge the patent. *Id.* Similarly, it would be unreasonable to either remove the '099 patent

from the Orange Book, as requested by Organon, or require a change from paragraph IV certification to section viii statement for mirtazapine ANDA applicants on the basis of a district court decision of non-infringement, where that decision was the result of the ANDA applicant's submission of a paragraph IV certification and successful litigation of the patent claim. In the normal course, FDA would require ANDA applicants with paragraph IV certifications to maintain the certification and leave the patent in the Orange Book for the 180-day period beginning with the court decision, even when the patent holder requests that the patent be removed from the Orange Book, as has happened with Organon.[1]

In the gabapentin case, Torpharm prevailed on January 16, 2003, in its paragraph IV litigation on the '479 patent in *Warner-Lambert* and thus might appear to be entitled to exclusivity. Thus, although Pfizer notified FDA on January 17, 2003, that it agreed to withdraw the '479 patent, FDA reexamined, in its January 28 letter, Torpharm's entitlement to 180-day exclusivity on that patent before delisting it. See 21 C.F.R. § 314.94 (a)(12)(viii)(B). As noted in FDA's January 28 letter, Pfizer clarified in its December 13 letter that the '479 patent claims the use of gabapentin to treat neurodegenerative diseases, not epilepsy. All of the relevant ANDAs seek approval for gabapentin products labeled for use in treating epilepsy. In light of Pfizer's December 13 clarification, no gabapentin ANDA applicant could retain a paragraph IV certification to the '479 patent. This conclusion was consistent with Judge Huvelle's findings. As FDA pointed out in its January 28 letter, if the '479 patent had remained in the Orange Book, Judge Huvelle's decision would have enabled every gabapentin ANDA applicant to submit a section viii statement to that patent. Thus, even if Torpharm could retain its paragraph IV certification, every other ANDA applicant could change a paragraph IV certification to a section viii statement, and thus deny Torpharm any exclusivity.

Therefore, the agency reaffirms that no ANDA applicants are eligible for exclusivity as to the now delisted '479 patent for gabapentin. Moreover, the '099 patent will remain in the Orange Book for the 180-day period following the district court decision, and mirtazapine ANDA applicants remain eligible for exclusivity as to that patent.

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[1] The mirtazapine ANDAs are governed by the "new" definition of the court decision trigger, which is described in FDA's Guidance *Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, March 2000. As to mirtazapine, the December 18, 2002, district court decision in *Organon v. Teva* triggers the running of exclusivity. In contrast, if any gabapentin ANDA applicant were eligible for exclusivity as to the '479 patent, such exclusivity would have been triggered by the *Warner-Lambert* appellate decision, as the gabapentin ANDAs are governed by the "old" definition of court decision as described in the guidance.

If you have questions regarding these issues, please contact Ms. Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, (301) 827-5845.

Sincerely yours,

Gary J. Buehler
Director
Office of Generic Drugs
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ANDA 75-360
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3/24/03

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